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233:54)

(52) UK CL (Edition L)

C2C CAA CQN CQT CRA CRE CUL C1173 C1175  
C1390 C1420 C1432 C1470 C1510 C1530 C200  
C213 C214 C215 C22Y C220 C225 C226 C227  
C246 C25Y C250 C251 C252 C253 C254 C255  
C256 C28X C30Y C31Y C311 C314 C339 C34Y  
C340 C342 C35Y C351 C355 C36Y C364 C366  
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C552 C604 C613 C62X C624 C625 C627 C628  
C65X C652 C658 C665 C697 C699 C70Y C80Y  
C802  
U1S S1318 S1321 S2414 S2415 S2416

(56) Documents cited

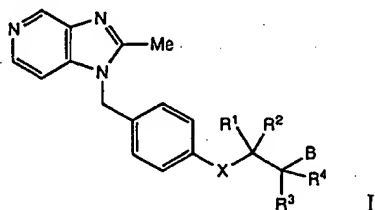
WO 91/17157 A

(58) Field of search

UK CL (Edition L) C2C CQN CQT CRA CRE CUL  
INT CL<sup>5</sup> C07D  
Online database: CAS ONLINE

(54) 1H-2-Methylimidazo(4,5-c)pyridinyl derivatives as PAF antagonists

(57) Compounds of general formula I;



wherein:

X represents a  $-C(=O)-$ ,  $-C(=S)-$ ,  $-S(->O)-$  or  $-S(=O)_2-$  group;

$R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  each independently represents hydrogen or one of various defined substituents or any combination of  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  together with the atoms to which they are attached form a 5 to 8 membered heterocyclic ring;

or any combination of  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  together with the carbon atom to which they are attached form a  $C_3$ - $C_8$  cycloalkyl ring;

B represents a) a  $-(CH_2)_m$ A group wherein m is 0 or 1 and the group A represents a 5- or 6-membered heterocyclic ring, which heterocyclic ring may be optionally fused to a benzene ring or to a further 5-, 6- or 7- membered heterocyclic ring containing one or more nitrogen atoms, wherein at least one of the said heterocyclic rings may also contain an oxygen or sulphur atom, and wherein any of the rings may be optionally substituted with one or more of certain defined substituents,

b) a  $ZR^8$  group wherein Z is  $-C(=O)-$ ,  $-C(=O)O-$ ,  $-C(=O)S-$ ,  $-CH_2O-$ ,  $-CH_2OC(=O)-$ ,  $-C(=S)-$ ,  $-C(=S)O-$ ,  $-CH_2S-$ ,  $-CH_2OC(=O)C(=O)O-$ ,  $-CH_2OSO_2-$ ,  $-NHC(=O)O-$ ,  $-CH_2OC(=O)NH-$  or  $-CH_2C(=O)O-$  group and  $R^8$  is hydrogen or one of certain defined organic groups.

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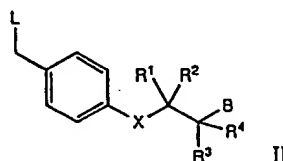
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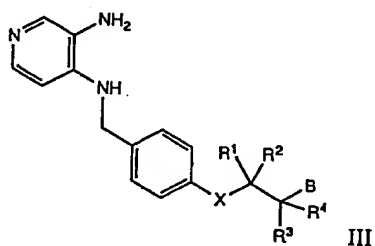
c) a  $-\text{CH}_2\text{NR}^9\text{R}^{10}$  group or a  $-\text{CONR}^9\text{R}^{10}$  group wherein each of  $\text{R}^9$  and  $\text{R}^{10}$  is independently hydrogen,  $-\text{C}_1-\text{C}_6$  alkyl,  $-\text{C}_3-\text{C}_8$  cycloalkyl, pyridinyl, a group D or  $\text{R}^9$  and  $\text{R}^{10}$  together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring; D being a defined aryl or aralkyl group,

and their pharmaceutically and veterinarily acceptable acid addition salts and hydrates are *antagonists of platelet activating factor (PAF)* and as such are useful in the *treatment or amelioration of various diseases or disorders mediated by PAF*.

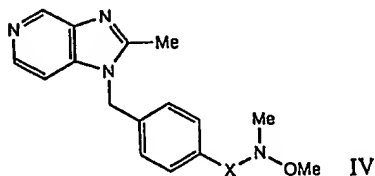
Precursors of the above compounds have the formulae:-



wherein L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy,



and



1H-2-Methylimidazo[4,5-c]pyridinyl derivatives as PAF antagonists

This invention relates primarily to novel compounds which are antagonists of platelet activating factor.

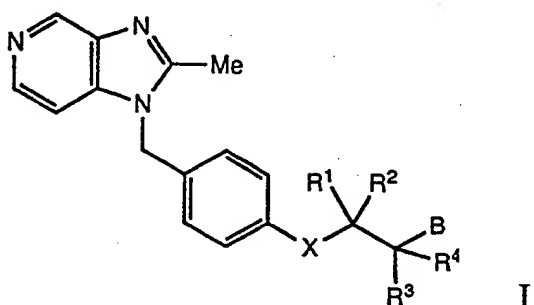
Platelet Activating Factor (PAF) is a bioactive phospholipid which has been identified as 1-*O*-hexadecyl/octadecyl-2-acetyl-*sn*-glyceryl-3-phosphoryl choline. PAF is released directly from cell membranes and mediates a range of potent and specific effects on target cells resulting in a variety of physiological responses which include hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, and increased vascular permeability (oedema/erythema). It is known that these physiological effects occur in many inflammatory and allergic diseases and PAF has been found to be involved in a number of such conditions including asthma, endotoxin shock, glomerulonephritis, immune regulation, transplant rejection, gastric ulceration, psoriasis, embryo implantation and cerebral, myocardial and renal ischemia. Thus the compounds of the invention, by virtue of their ability to antagonise the actions of PAF, should be of value in the treatment of any of the above conditions.

Compounds that have been disclosed as possessing activity as PAF antagonists include compounds which are structurally related to the PAF molecule such as glycerol derivatives (EP-A-0238202), and heterocyclic compounds such as 5-oxy derivatives of tetrahydrofuran (US-4,888,337) and 2,5-diaryl tetrahydrofurans (EP-A-0144804). Recently a more potent 2,5-diaryl tetrahydrofuran derivative, (*trans*)-2-(3-methoxy-5-methylsulphonyl-4-propoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (L-659,989) has been disclosed (EP-A-0199324). In our International patent application No. WO 91/17157 we disclose a series of  $\gamma$ -butyrolactol derivatives as PAF antagonists. The compounds of WO 91/17157 differ from the 5-oxy derivatives of tetrahydrofuran described in US-4,888,337 and from the 2,5-diaryl tetrahydrofurans such as L-659,989, in that they feature an appended heterocycle with an unsubstituted sp<sup>2</sup> nitrogen atom. There are a number of other PAF antagonists, in addition to those of WO 91/17157, for which the presence of a heterocyclic sp<sup>2</sup> nitrogen atom appears to be an important requirement for activity (Whittaker, M., Curr. Opin. Thera. Patents 2(5), 583-623 (1992)).

For the compounds of the present invention the presence of a heterocyclic group

possessing an unsubstituted  $sp^2$  nitrogen atom is also a requirement for PAF antagonist activity. However, the present invention provides novel and useful substituted phenyl sulphonyl and phenylcarbonyl derivatives and their pharmaceutically acceptable acid addition salts, and pharmaceutical uses thereof as PAF antagonists.

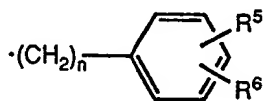
According to a first aspect of the invention there is provided a compound of general formula I;



wherein:

X represents a  $-C(=O)-$ ,  $-C(=S)-$ ,  $-S(\rightarrow O)-$  or  $-S(=O)_2-$  group;

$R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  each independently represents hydrogen,  $-C_1-C_6$  alkyl optionally substituted by one or more halogen atoms,  $-C_2-C_6$  alkenyl,  $-C_2-C_6$  alkynyl,  $-(C_1-C_6 \text{ alkyl})CO_2C_1-C_6 \text{ alkyl}$ ,  $-(C_1-C_6 \text{ alkyl})SC_1-C_6 \text{ alkyl}$ ,  $-(C_1-C_6 \text{ alkyl})OC_1-C_6 \text{ alkyl}$ ,  $-(C_1-C_6 \text{ alkyl})N(C_1-C_6 \text{ alkyl})_2$ ,  $-C_3-C_8$  cycloalkyl,  $-C_4-C_8$  cycloalkenyl,  $-(C_1-C_6 \text{ alkyl})C_3-C_8$  cycloalkyl,  $-(C_1-C_6 \text{ alkyl})C_4-C_8$  cycloalkenyl,  $-(C_1-C_6 \text{ alkyl})OC_3-C_8$  cycloalkyl,  $-(C_1-C_6 \text{ alkyl})OC_4-C_8$  cycloalkenyl,  $-(C_1-C_6 \text{ alkyl})SC_3-C_8$  cycloalkyl,  $-(C_1-C_6 \text{ alkyl})SC_4-C_8$  cycloalkenyl, a side chain of a naturally occurring amino acid or a group D wherein D represents a group:



wherein  $n$  is an integer from 0 to 3, and each of  $R^5$  and  $R^6$  is independently hydrogen,  $-C_1-C_6$  alkyl,  $-C_2-C_6$  alkenyl,  $-C_2-C_6$  alkynyl, halogen,  $-CN$ ,  $-CO_2H$ ,  $-CO_2C_1-C_6 \text{ alkyl}$ ,  $-CONH_2$ ,  $-CONHC_1-C_6 \text{ alkyl}$ ,  $-CONH(C_1-C_6 \text{ alkyl})_2$ ,  $-CHO$ ,  $-CH_2OH$ ,  $-CF_3$ ,  $-OC_1-C_6 \text{ alkyl}$ ,  $-SC_1-C_6 \text{ alkyl}$ ,  $-SOC_1-C_6 \text{ alkyl}$ ,  $-SO_2C_1-C_6 \text{ alkyl}$ ,  $-NH_2$  or  $-NHCOMe$ ;

or any combination of  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  together with the atoms to which they

are attached form a 5 to 8 membered heterocyclic ring;

or any combination of  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  together with the carbon atom to which they are attached form a C<sub>3</sub>-C<sub>8</sub> cycloalkyl ring;

B represents a) a  $-(CH_2)_m A$  group wherein m is an integer from 0 to 1 and the group A represents a 5- or 6-membered heterocyclic ring, which heterocyclic ring may be optionally fused to a benzene ring or to a further 5-, 6- or 7-membered heterocyclic ring containing one or more nitrogen atoms, wherein at least one of the said heterocyclic rings may also contain an oxygen or sulphur atom, and wherein any of the rings may be optionally substituted with one or more substituents selected from hydrogen, halogen, -C<sub>1</sub>-C<sub>4</sub> perfluoroalkyl, hydroxyl, carbonyl, thiocarbonyl, carboxyl, -CONH<sub>2</sub>, a group -D wherein D is as defined above, -R<sup>7</sup>, -OR<sup>7</sup>, -SR<sup>7</sup>, -SOR<sup>7</sup>, -SO<sub>2</sub>R<sup>7</sup>, -NHR<sup>7</sup>, -NR<sup>7</sup>R<sup>7</sup>, -CO<sub>2</sub>R<sup>7</sup> or -CONHR<sup>7</sup> wherein R<sup>7</sup> is -C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>2</sub>-C<sub>6</sub> alkenyl, -C<sub>2</sub>-C<sub>6</sub> alkynyl, -C<sub>3</sub>-C<sub>8</sub> cycloalkyl or -C<sub>4</sub>-C<sub>8</sub> cycloalkenyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxyl, amino, carboxyl, -C<sub>1</sub>-C<sub>4</sub> perfluoroalkyl, -C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>2</sub>-C<sub>6</sub> alkenyl, -C<sub>2</sub>-C<sub>6</sub> alkynyl, -C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, -OC<sub>1</sub>-C<sub>6</sub> alkyl, -SC<sub>1</sub>-C<sub>6</sub> alkyl, tetrazol-5-yl, a group -D wherein D is as defined above or a heteroaryl or heteroarylmethyl group;

b) a ZR<sup>8</sup> group wherein Z is -C(=O)-, -C(=O)O-, -C(=O)S-, -CH<sub>2</sub>O-, -CH<sub>2</sub>OC(=O)-, -C(=S)-, -C(=S)O-, -CH<sub>2</sub>S-, -CH<sub>2</sub>OC(=O)C(=O)O-, -CH<sub>2</sub>OSO<sub>2</sub>-, -NHC(=O)O-, -CH<sub>2</sub>OC(=O)NH- or -CH<sub>2</sub>C(=O)O- group and R<sup>8</sup> is hydrogen, -C<sub>1</sub>-C<sub>18</sub> alkyl, -C<sub>2</sub>-C<sub>18</sub> alkenyl, -C<sub>2</sub>-C<sub>18</sub> alkynyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)OC<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)SC<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)O(C<sub>1</sub>-C<sub>6</sub> alkyl)OC<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -C<sub>4</sub>-C<sub>8</sub> cycloalkenyl, a group D as defined above or a group A as defined above;

c) a -CH<sub>2</sub>NR<sup>9</sup>R<sup>10</sup> group or a -CONR<sup>9</sup>R<sup>10</sup> group wherein each of R<sup>9</sup> and R<sup>10</sup> is independently hydrogen, -C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>3</sub>-C<sub>8</sub> cycloalkyl, pyridinyl, a group D as defined above or R<sup>9</sup> and R<sup>10</sup> together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

Hereafter in this specification the term "compound" includes "salt" or "hydrate"

unless the context requires otherwise.

As used herein the term "halogen" or its abbreviation "halo" means fluoro, chloro, bromo or iodo.

As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to six carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl.

As used herein the term "C<sub>1</sub>-C<sub>18</sub> alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to eighteen carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, decyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, and octadecyl. From one to six carbon atoms may be preferred.

As used herein the term "C<sub>2</sub>-C<sub>6</sub> alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C<sub>2</sub>-C<sub>18</sub> alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to eighteen carbon atoms and having in addition one or more double bonds, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl, 2-methyl-2-propenyl, geranyl, and farnesyl. From two to six carbon atoms may be preferred.

As used herein, the term "C<sub>1</sub>-C<sub>4</sub> perfluoroalkyl" refers to straight chain or branched chain groups having from one to four carbon atoms and substituted by more than one fluorine atom. This term would include for example, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoro-n-propyl, hexafluoro-i-propyl, septafluoro-n-propyl, septafluoro-i-propyl, 4,4,4-trifluoro-n-butyl, nonafluoro-n-butyl, nonafluoro-sec-butyl and nonafluoro-i-butyl.

As used herein the term "OC<sub>1</sub>-C<sub>6</sub> alkyl" refers to straight chain or branched chain alkoxy groups having from one to six carbon atoms. Illustrative of such alkoxy

groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy and hexoxy.

As used herein the term "SC<sub>1</sub>-C<sub>6</sub> alkyl" refers to straight chain or branched chain alkylthio groups having from one to six carbon atoms. Illustrative of such alkyl groups are methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio and hexylthio.

As used herein, the term "C<sub>3</sub>-C<sub>8</sub> cycloalkyl" refers to an alicyclic group having from 3 to 8 carbon atoms. Illustrative of such cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term "C<sub>4</sub>-C<sub>8</sub> cycloalkenyl" refers to an alicyclic group having from 4 to 8 carbon atoms and having in addition one or more double bonds. Illustrative of such cycloalkenyl groups are cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein, the term "side chain of a naturally occurring amino acid" includes the side chains of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, glycine, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine,  $\alpha$ -amino adipic acid,  $\alpha$ -amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine,  $\alpha$ -methylserine, ornithine, pipecolic acid, and thyroxine. The amino acid side chains may be protected; for example the carboxyl groups of aspartic acid, glutamic acid and  $\alpha$ -amino adipic acid may be esterified (for example as a C<sub>1</sub>-C<sub>6</sub> alkyl ester), the amino groups of lysine, ornithine, 5-hydroxylysine, 4-hydroxyproline may be converted to amides (for example as a COC<sub>1</sub>-C<sub>6</sub> alkyl amide) or carbamates (for example as a C(=O)OC<sub>1</sub>-C<sub>6</sub> alkyl or C(=O)OCH<sub>2</sub>Ph carbamate), the hydroxyl groups of 5-hydroxylysine, 4-hydroxyproline, serine, threonine, tyrosine, 3,4-dihydroxyphenylalanine, homoserine,  $\alpha$ -methylserine and thyroxine may be converted to ethers (for example a C<sub>1</sub>-C<sub>6</sub> alkyl or a (C<sub>1</sub>-C<sub>6</sub> alkyl)phenyl ether) or esters (for example a C(=O)C<sub>1</sub>-C<sub>6</sub> alkyl ester) and the thiol group of cysteine may be converted to thioethers (for example a C<sub>1</sub>-C<sub>6</sub> alkyl thioether) or thioesters (for example a C(=O)C<sub>1</sub>-C<sub>6</sub> alkyl thioester). The stereochemistry at the carbon atom to which the amino acid side chain is attached may be either D or L.

As used herein, the term "5- or 6-membered heterocyclic ring" refers to such rings having from 5 to 6 atoms in the ring wherein the heteroatom(s) may be

one or more nitrogen, oxygen or sulphur atoms. For example heterocycles containing nitrogen, oxygen, or sulphur alone or containing two nitrogen atoms, a nitrogen and an oxygen atom, a nitrogen and a sulphur atom, two nitrogen atoms and an oxygen atom, two nitrogen atoms and a sulphur atom, three nitrogen atoms or four nitrogen atoms.

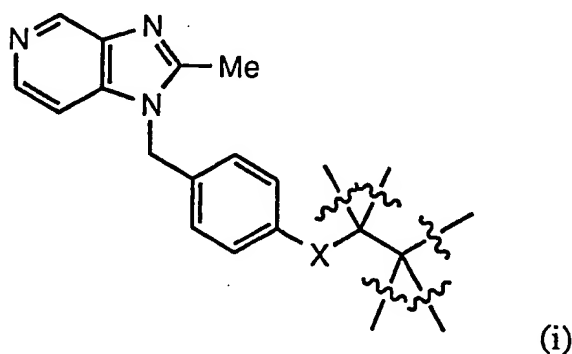
As used herein, the term "nitrogen-containing heterocyclic ring" refers to an aromatic or alicyclic ring comprising one or more nitrogen atoms and optionally one or more other heteroatoms. Illustrative of such rings are pyrrolidine, piperidine, hexamethyleneimine, heptamethylenimine, morpholine and piperazine.

In compounds of this invention, the presence of several asymmetric carbon atoms gives rise to diastereoisomers, each of which consists of two enantiomers, with the appropriate R or S stereochemistry at each chiral center. The invention is understood to include all such diastereoisomers, their optically active enantiomers and mixtures thereof.

The term "pharmaceutically or veterinarily acceptable acid addition salt" refers to a salt prepared by contacting a compound of formula (I) with an acid whose anion is generally considered suitable for human or animal consumption.

Examples of pharmaceutically and/or veterinarily acceptable acid addition salts include the hydrochloride, sulphate, phosphate, acetate, propionate, lactate, maleate, succinate and tartrate salts.

It is considered that the main structural feature of compounds of general formula I that is particularly significant in providing their PAF antagonist activity, is the subunit (i);



There may be considerable variation of the substituent groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>

and B without loss of such activity. Any of the wide range of substituents R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and B defined above may be used with retention of PAF antagonist activity. However, the preferred substituent for the group R<sup>3</sup> is the side chain of the amino acid L-leucine (i.e. sec-butyl) and for the group R<sup>4</sup> is a hydrogen atom.

The 1H-2-methylimidazo[4,5-c]pyridinyl group of the subunit is an important requirement for PAF antagonist activity. However, it is expected that PAF antagonist activity may be found in compounds analogous to those of general formula I above, wherein the 1H-2-methylimidazo[4,5-c]pyridinyl group is replaced by a different sp<sup>2</sup> nitrogen heterocycle. The variety of sp<sup>2</sup> nitrogen heterocycles that could provide PAF antagonist activity include those disclosed in our patent application WO 91/17157 and those recently described by Whittaker (Whittaker, M., Curr. Opin. Thera. Patents 2(5), 583-623 (1992)) and Cooper (Cooper, K., *et al.*, J. Med. Chem. 35(17), 3115-3129 (1992)). The exact nature of the interaction of the sp<sup>2</sup> nitrogen heterocycle and the receptor has not been determined, but it would appear that it is important for the heterocycle to possess at least one unsubstituted sp<sup>2</sup> nitrogen atom within the heterocyclic ring.

Although in this application the only substituents claimed for the subunit (i) are R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and B it is understood that the introduction of further substituents on the 2-methylimidazo[4,5-c]pyridinyl group, the benzylic carbon atom and/or the 1,4-disubstituted phenyl ring of subunit (i) will lead to compounds that retain PAF antagonist activity.

Preferred compounds include those in which, independently or in any compatible combination;

X represents a -C(=O)- group or a -S(=O)<sub>2</sub>- group;

R<sup>1</sup> represents a hydrogen atom, a -C<sub>1</sub>-C<sub>6</sub> alkyl (for example methyl or ethyl) group, a -C<sub>2</sub>-C<sub>6</sub> alkenyl (for example allyl) group or a -(C<sub>1</sub>-C<sub>6</sub> alkyl)CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl (for example ethoxycarbonylmethyl) group;

R<sup>2</sup> represents a hydrogen atom or a -C<sub>1</sub>-C<sub>6</sub> alkyl (for example methyl or ethyl) group;

R<sup>3</sup> represents a side chain of a naturally occurring amino acid (for example the side chain of leucine or isoleucine), a -(C<sub>1</sub>-C<sub>6</sub> alkyl)C<sub>3</sub>-C<sub>8</sub> cycloalkyl (for

example cyclopropylmethyl or cyclopentyl methyl) group or a group D;

R<sup>4</sup> represents a hydrogen atom;

in the group D, n represents an integer of 1;

R<sup>5</sup> represents a hydrogen atom or a halogen (for example fluorine) atom;

R<sup>6</sup> represents a hydrogen atom;

B represents a  $-(CH_2)_m A$  group, a  $ZR^8$  or a  $-CONR^9R^{10}$  group;

m represents an integer of 0;

A represents a furanyl (for example furan-2-yl) group, an oxadiazolyl (for example 1,2,4-oxadiazol-5-yl) group, a benzthiazolyl (for example benzothiazol-2-yl) group or a thienyl (for example thien-2-yl) group;

Z represents a  $-C(=O)O-$  group, a  $-CH_2O-$  group, a  $-CH_2OC(=O)-$  group or a  $-CH_2OC(=O)NH-$  group;

R<sup>7</sup> represents a  $-C_1-C_6$  alkyl (for example ethyl) group;

R<sup>8</sup> represents a  $-C_1-C_{18}$  alkyl (for example methyl, ethyl, i-propyl or hexadecyl) group;

R<sup>9</sup> represents a pyridinyl (for example 2-pyridinyl) group;

R<sup>10</sup> represents a hydrogen atom.

Particularly preferred compounds include:

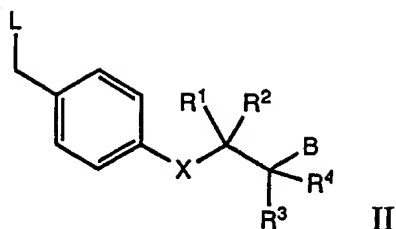
1. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate,
2. 1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)propane,
3. 1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)butane,
4. 1-Ethoxy-2-benzyl-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)pentane,
5. 1-Methyl-1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-

6. sulphonyl)-2-(2-methylpropyl)-2-(furan-2-yl)-4-methylpentane,
6. 3-Acetoxy-5-methyl-2-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)hexane,
7. 3-Ethylcarbamoyl-5-methyl-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)hexane,
8. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylcarbonyl)-2-(2-methylpropyl)butanoate,
9. 1-(4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)-2-(3-ethyl-1,2,4-oxadiazol-5-yl)-4-methylpentane,
10. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-4-benzthiazol-2-yl-5-methylhexanoate,
11. 1-Heptadecanoyl-2-(2-cyclopentylmethyl)-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)-3-methylbutane,
12. N-2-Pyridinyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(1-methylpropyl)propionamide,
13. i-Propyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(cyclopropylmethyl)hex-5-enoate,
14. 1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-thienyl)-3-(4-fluorophenyl)ethane,
15. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)butanoate.

Compounds of general formula I may be prepared by any suitable method known in the art and/or by the following process, which itself forms part of the invention.

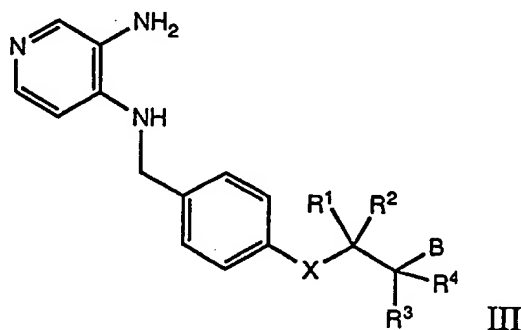
According to a second aspect of the invention, there is provided a process for preparing a compound of general formula I as defined above, the process comprising:

- (a) treating 2-methylimidazo[4,5-c]pyridine with a suitable base (e.g. sodium hydride, potassium hydride or sodium bis(trimethylsilyl)amide), followed by a benzyl derivative of general formula II



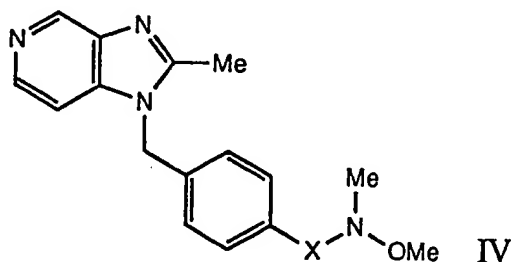
wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and B are as defined in general formula I, and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy; or

(b) treating a diamino derivative represented by general formula III



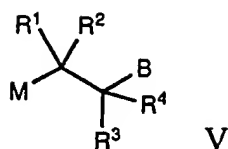
wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and B are as defined in general formula I, with acetic acid or a suitable derivative thereof; or

(c) treating an amido or sulphonamido derivative represented by general formula IV



wherein X is as defined in general formula I, with a compound of general formula V

11



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and B are as defined in general formula I, and M is MgBr or Li; or

(d) optionally after step (a), step (b) or step (c) converting, in one or a plurality of steps, a compound of general formula I into another compound of general formula I.

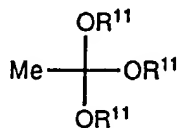
The reaction of step (a) can for preference be conducted in an aprotic solvent (e.g. tetrahydrofuran, N,N-dimethylformamide or acetonitrile) to yield compounds of general formula I. The reaction can yield an isomeric mixture, which is separated by chromatography to yield compounds of general formula I.

In step (b), derivatives of acetic acid, which are suitable substrates for the reaction include acetyl halides of general formula VI



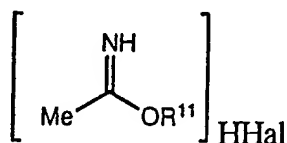
VI

wherein Hal is fluoride, chloride, bromide or iodide; trialkylorthoesters of general formula VII



VII

wherein  $R^{11}$  is  $-C_1-C_6$  alkyl; imino ether salts of general formula VIII



VIII

wherein  $R^{11}$  is  $-C_1-C_6$  alkyl and Hal is fluoride, chloride, bromide, or iodide, or acetic anhydride. Acetyl halides of general formula VI, trialkylorthoesters of general formula VII and imino ether salts of general formula VIII are available

in the art or can be prepared by methods analogous to those known in the art

The reaction of step (c) can for preference be conducted in an aprotic solvent (e.g. tetrahydrofuran) to yield compounds of general formula I.

By means of step (d) certain compounds of general formula I may be converted into another compound of general formula I; by

(i) treating a compound of general formula I wherein  $R^1$  represents a hydrogen atom with a base, such as lithium diisopropylamide, in an aprotic solvent (e.g. tetrahydrofuran or diethyl ether) followed by an electrophile of the general formula IX

LR<sup>1</sup>

IX

wherein  $R^1$  is -C<sub>1</sub>-C<sub>6</sub> alkyl, -C<sub>3</sub>-C<sub>6</sub> alkenyl, -CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, -SC<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)SC<sub>1</sub>-C<sub>6</sub> alkyl, -(C<sub>1</sub>-C<sub>6</sub> alkyl)OC<sub>1</sub>-C<sub>6</sub> alkyl and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoro-methanesulphonyloxy. Electrophiles of the general formula IX are available in the art or can be prepared by methods analogous to those known in the art, or:

(ii) by means of step (d) compounds of general formula I wherein B is a -CO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup> group wherein R<sup>9</sup> and R<sup>10</sup> are as defined in general formula I, may be prepared by the following methods;

(a) by treatment of a compound of general formula I wherein B is a -CO<sub>2</sub>R<sup>8</sup> group wherein R<sup>8</sup> is a benzyl group with hydrogen in the presence of a noble metal catalyst (eg 10% palladium on charcoal) to give a carboxylic acid which is then treated with an amine of general formula HNR<sup>9</sup>R<sup>10</sup> in the presence of a coupling reagent (e.g. 1,3-dicyclohexylcarbodiimide); or

(b) by treatment of a compound of general formula I wherein B is a -CO<sub>2</sub>R<sup>8</sup> group wherein R<sup>8</sup> is a lower alkyl with a dimethylaluminium amide of general formula X

(Me)<sub>2</sub>AlNR<sup>9</sup>R<sup>10</sup> X

wherein  $R^9$  and  $R^{10}$  are as defined in general formula I, which is prepared *in situ* from trimethylaluminium and an amine of general formula  $HNR^9R^{10}$ ; or

(iii) also by means of step (d) certain compounds of general formula I wherein B is a  $ZR^8$  group wherein Z is  $-CH_2O-$  and  $R^8$  is hydrogen may be prepared by treatment of a compound of general formula I wherein B is a  $ZR^8$  group wherein Z is  $-C(=O)O-$  and  $R^8$  is other than hydrogen with a suitable reducing agent (e.g. lithium aluminium hydride); or

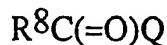
(iv) also by means of step (d) certain compounds of general formula I wherein B is a  $ZR^8$  group wherein Z is  $-CH_2O-$  and  $R^8$  is other than hydrogen may be prepared by treatment of a compound of general formula I wherein B is a  $ZR^8$  group wherein Z is  $-CH_2O-$  and  $R^8$  is hydrogen with a suitable base in an aprotic solvent followed by an electrophile of general formula XI



XI

wherein  $R^8$  is  $-C_1-C_{18}$  alkyl,  $-C_3-C_{18}$  alkenyl,  $-C_3-C_{18}$  alkynyl,  $-(C_1-C_6 \text{ alkyl})OC_1-C_6 \text{ alkyl}$ ,  $-(C_1-C_6 \text{ alkyl})SC_1-C_6 \text{ alkyl}$ ,  $-(C_1-C_6 \text{ alkyl})O(C_1-C_6 \text{ alkyl})OC_1-C_6 \text{ alkyl}$ ,  $-C_3-C_8$  cycloalkyl,  $-C_4-C_8$  cycloalkenyl, or a group D wherein n is an integer from 1 to 3 and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy. Electrophiles of the general formula XI are available in the art or can be prepared by methods analogous to those known in the art; or

(v) also by means of step (d) certain compounds of general formula I wherein B is a  $ZR^8$  group wherein Z is  $-CH_2OC(=O)-$  and  $R^8$  is other than hydrogen may be prepared by treatment of a compound of general formula I wherein B is a  $ZR^8$  group wherein Z is  $-CH_2O-$  and  $R^8$  is hydrogen with a suitable carboxylic acid derivative of general formula XII



XII

wherein Q is a hydrogen, halide or a  $-(O=)CR^8$  group. The conditions for this reaction will depend on the nature of the group Q and will be apparent to one skilled in the art. Carboxylic acids of the general formula XII are available in the art or can be prepared by methods analogous to those known in the art; or

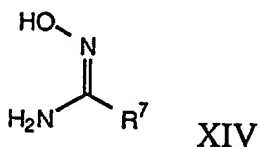
(vi) also by means of step (d) certain compounds of general formula I wherein B is a  $ZR^8$  group wherein Z is  $-\text{CH}_2\text{OC}(=\text{O})\text{NH}-$  and  $R^8$  is other than hydrogen may be prepared by treatment of a compound of general formula I wherein B is a  $ZR^8$  group wherein Z is  $-\text{CH}_2\text{O}-$  and  $R^8$  is hydrogen with an isocyanate of general formula XIII



XIII

wherein  $R^8$  is as defined in general formula I. Isocyanates of the general formula XIII are available in the art or can be prepared by methods analogous to those known in the art; or

(vii) also by means of step (d) certain compounds of general formula I wherein B is a 1,2,4-oxadiazol-5-yl group may be prepared by treatment of a compound of general formula I wherein B is a  $-\text{CO}_2\text{H}$  group with pentafluorophenol and a coupling agent such as N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide in a solvent such as dichloromethane. The resulting pentafluorophenyl ester is treated with an amide oxime of general formula XIV



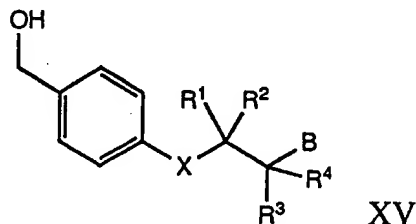
wherein  $R^7$  is as defined in general formula I in a suitable aprotic solvent (e.g. chloroform), followed by cyclisation under Dean-Stark conditions in suitable solvent (e.g. xylene, toluene, benzene or ethyl acetate). The cyclisation may be aided by the addition of activated molecular sieves. Amide oximes of general formula XIV are known in the art or may be prepared by methods analogous to those known in the art; or

(viii) also by means of step (d) certain compounds of general formula I wherein X is a sulphone group may be prepared by treating a compound of general formula I, wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and B are as defined in general formula I and X represents  $-\text{S}-$ , with a suitable oxidising agent (for example metachloroperbenzoic acid); or

(ix) also by means of step (d) certain compounds of general formula I wherein X is a thiocarbonyl group may be prepared by treating a compound of general

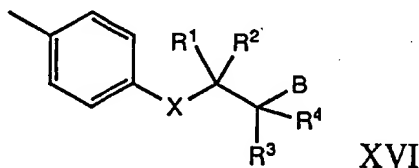
formula I, wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and B are as defined in general formula I and X represents a  $-(C=O)-$  group, with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide.

Benzyl derivatives of general formula II may be prepared by treatment of a compound of general formula XV

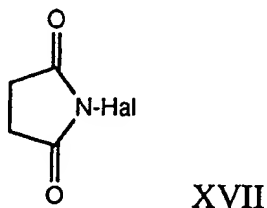


wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and B are as defined in general formula I, with thionylchloride.

In a second method, benzyl derivatives of general formula II wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and B are as defined in general formula I, may also be prepared by treatment of a compound of general formula XVI



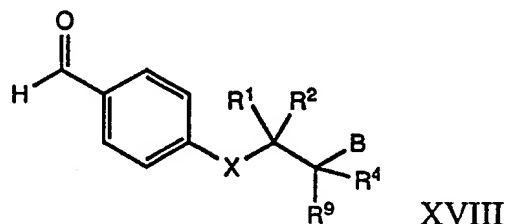
wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and B are as defined in general formula I, with a compound of general formula XVII



wherein Hal is fluoride, chloride, bromide or iodide, in the presence of a suitable radical initiator (e.g. 2,2'-azobis(2-methylpropionitrile)) in a suitable solvent (e.g. benzene or carbon tetrachloride). Compounds of general formula XVII are

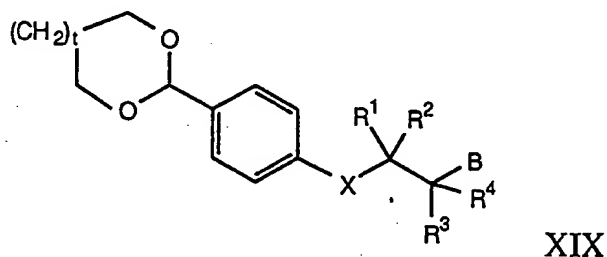
available in the art.

Compounds of general formula XV wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and B are as defined in general formula I, may be prepared by the reduction of a compound of general formula XVIII



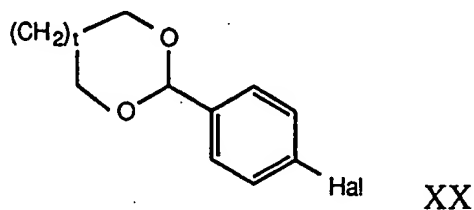
wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and B are as defined in general formula I, with a reducing agent such as lithium aluminium hydride

Compounds of general formula XVIII may be prepared by treating an acetal derivative represented by general formula XIX

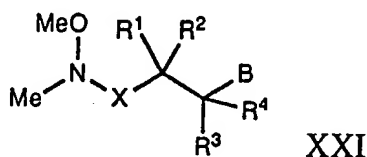


wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and B are as defined in general formula I and t is an integer of 0 or 1, with a suitable acid (for example hydrochloric acid), in a suitable solvent, such as acetone.

Compounds of general formula XIX may be prepared by treating a haloarenyl derivative represented by general formula XX

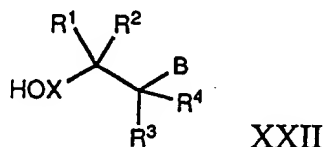


wherein Hal is fluoride, chloride, bromide or iodide, with a suitable metallating agent (for example t-butyl lithium), followed by a compound of general formula XXI



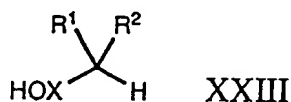
wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and B are as defined in general formula I. Compounds of general formula XX are acetals of commercially available p-halobenzaldehydes.

Compounds of general formula XXI may be prepared by treating a carboxylic or sulphonic acid derivative represented by general formula XXII

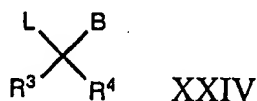


wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and B are as defined in general formula I, with a suitable activating agent (e.g. thionyl chloride), followed by a N,O-dimethylhydroxylamine hydrochloride in the presence of suitable base such as triethylamine.

Compounds of general formula XXII may be prepared by treating a carboxylic or sulphonic acid derivative represented by general formula XXIII



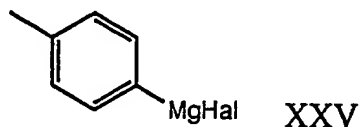
wherein R<sup>1</sup>, R<sup>2</sup> and X are as defined in general formula I, with a strong base (e.g. n-butyllithium), followed by a compound of general formula XXIV



wherein R<sup>3</sup>, R<sup>4</sup> and B are as defined in general formula I. Compounds of

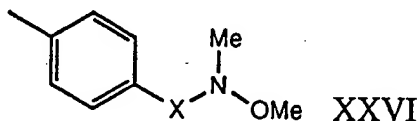
general formulae XXIII and XXIV are available in the art or may be prepared by methods known to those skilled in the art.

Compounds of general formula XVI may be prepared by treating a Grignard reagent represented by general formula XXV



wherein Hal is fluoride, chloride, bromide or iodide with a compound of general formula XXI wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and B are as defined in general formula I. Compounds of general formula XXV may be prepared from p-halotoluene and magnesium.

In a second method, compounds of general formula XVI may be prepared by treating a sulphonamide or carboxamide derivative of general formula XXVI

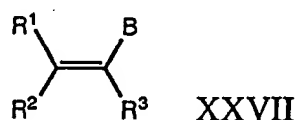


wherein X is as defined in general formula I, with a suitable metallo derivative of general formula V, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and B are as defined in general formula I, and M is MgBr or Li, in an aprotic solvent (e.g. tetrahydrofuran).

Compounds of general formula XVI wherein X is a sulphone group may be prepared by treating an aryl thio derivative represented by general formula XVI, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and B are as defined in general formula I and X represents -S-, with a suitable oxidising agent (for example metachloroperbenzoic acid).

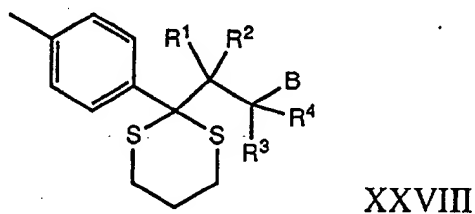
(Compounds of general formula XVI wherein X is a thiocarbonyl group may be prepared by treating a carbonyl compound of general formula XVI, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and B are as defined in general formula I and X represents a -(C=O)-group, with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide.

Compounds of general formula XVI, wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  are as defined in general formula I, X represents -S- and B represents a  $-\text{CO}_2R^8$  group wherein  $R^8$  is as defined in general formula I but is other than hydrogen, may be prepared by treating 4-methylthiophenol with a suitable base (e.g. sodium hydride), followed by a  $\alpha,\beta$ -unsaturated compound of general formula XXVII



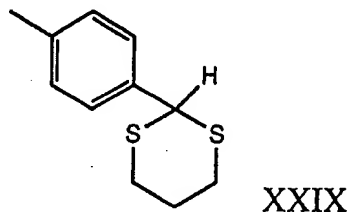
wherein  $R^1$ ,  $R^2$ ,  $R^3$  and B are as defined in general formula I and B represents a  $-\text{CO}_2R^8$  group wherein  $R^8$  is as defined in general formula I but is other than hydrogen, in a suitable aprotic solvent (e.g. tetrahydrofuran). Compounds of general formula XXVII are available in the art.

Compounds of general formula XVI wherein X represents a carbonyl group may be prepared by treating a dithiane derivative represented by general formula XXVIII



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and B are as defined in general formula I, with a suitable oxidant (e.g. mercury(II)).

Compounds of general formula XXVIII, wherein B represents a  $-\text{CO}_2R^8$  group wherein  $R^8$  is as defined in general formula I but is other than hydrogen, may be prepared by treating a dithiane derivative represented by formula XXIX



with a suitable base (for example n-butyl lithium), followed by a compound of

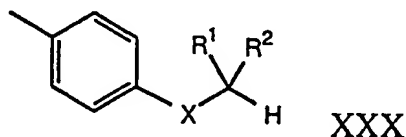
general formula XXVII wherein B represents a  $-\text{CO}_2\text{R}^8$  group wherein  $\text{R}^8$  is as defined in general formula I but is other than hydrogen. Compounds of formula XXIX is available in the art.

Compounds of general formula XVI wherein  $\text{R}^1$  is a hydrogen atom and B is a  $-\text{CO}_2\text{H}$  group may be prepared by the decarboxylation of a compound of general formula XVI, wherein  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are as defined in general formula I,  $\text{R}^1$  is a  $-\text{CO}_2\text{H}$  group and B is a  $-\text{CO}_2\text{H}$  group by heating in the presence of an acid or base catalyst.

Compounds of general formula XVI wherein  $\text{R}^1$  is a hydrogen atom and B is a  $-\text{CO}_2\text{C}_1\text{-C}_{18}$  alkyl group may be prepared by the esterification of a compound of general formula XVI, wherein  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are as defined in general formula I,  $\text{R}^1$  is a hydrogen atom and B is a  $-\text{CO}_2\text{H}$  group with the appropriate alcohol. The reaction may be catalysed by an acid catalysed or may be conducted by formation of an intermediate activated ester.

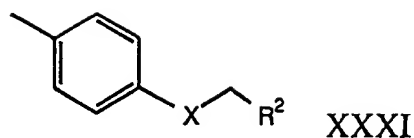
Compounds of general formula XVI wherein  $\text{R}^1$  is a  $-\text{CO}_2\text{H}$  group and B is a  $-\text{CO}_2\text{H}$  group may be prepared by the acid or base catalysed hydrolysis of a compound of general formula XVI, wherein  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are as defined in general formula I,  $\text{R}^1$  is a  $-\text{CO}_2\text{C}_1\text{-C}_6$  alkyl group and B is a  $-\text{CO}_2\text{C}_1\text{-C}_6$  alkyl group.

In another method, compounds of general formula XV may be prepared by treating a compound represented by general formula XXX

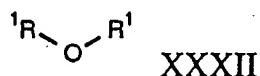


wherein  $\text{R}^1$  is a  $-\text{CO}_2\text{C}_1\text{-C}_6$  alkyl group and  $\text{R}^2$  and X are as defined in general formula I with a suitable base (e.g. potassium t-butoxide) in an aprotic solvent (e.g. N,N-dimethylformamide) followed by a compound of general formula XXIV.

Compounds of general formula XXX may be prepared by treating a compound of general formula XXXI

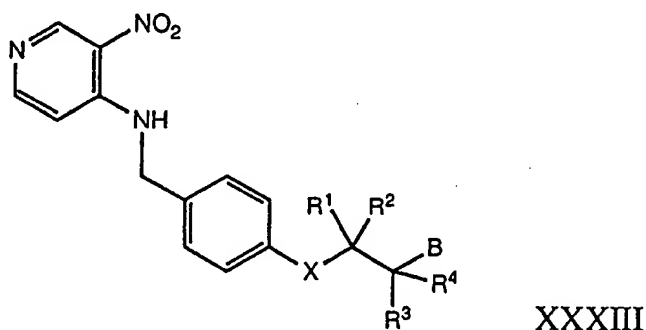


wherein X and R<sup>2</sup> is as defined in general formula I with a suitable base (e.g. lithium diisopropyl amide) in an aprotic solvent (e.g. tetrahydrofuran) followed by a compound of general formula XXXII



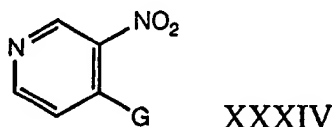
wherein R<sup>1</sup> is a -CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl group. Compounds of general formula XXXI and of general formula XXXII are available in the art or may be prepared by methods known to those skilled in the art.

Compounds of general formula III may be prepared by treating a nitro derivative represented by general formula XXXIII

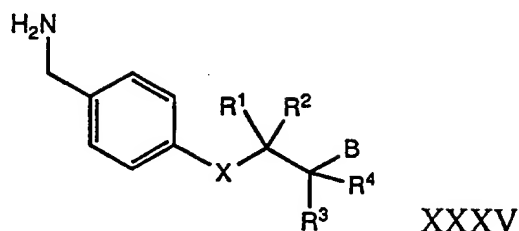


wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and B are as defined in general formula I, with a suitable reducing agent (for example hydrogen), in the presence of a catalyst such as palladium or platinum.

Substituted 1,2-nitroamines of general formula XXXIII may be prepared by a number of methods. The first of these methods involves the treatment of a nitro compound of general formula XXXIV

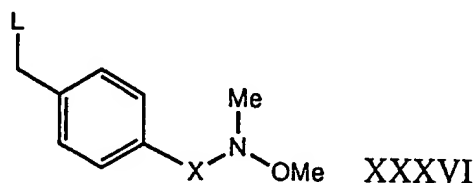


wherein G is halo or C<sub>1</sub>-C<sub>6</sub> alkoxy; is treated with an amino compound of general formula XXXV



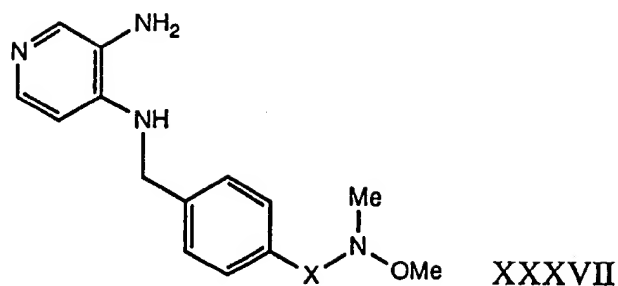
wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and B are as defined in general formula I. Nitro compounds of general formula XXXIV are available in the art or can be prepared by methods analogous to those known in the art. Amino compounds of general formula XXXV can be prepared by treatment of a compound of general formula II with hexamethylenetetramine followed by treatment with ethanolic hydrochloric acid or by sequential treatment of a compound of general formula II with sodium azide followed by triphenylphosphine in 'wet' tetrahydrofuran or by hydrogenation over a suitable catalyst.

Compounds of general formula IV may be prepared by treating 2-methylimidazo[4,5-c]pyridine with a suitable base (e.g. sodium hydride, potassium hydride or sodium bis(trimethylsilyl)amide), followed by a compound of general formula XXXVI



wherein X is as defined in general formula I and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy.

In a second procedure, compounds of general formula IV may be prepared by treatment of a diamino derivative represented by general formula XXXVII

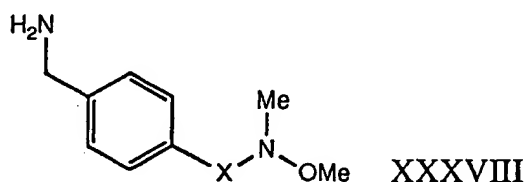


wherein X is as defined in general formula I, with acetic acid, acetic anhydride, an acetyl halide of general formula VI, a trialkylorthoester of general formula VII or an imino ether salt of general formula VIII acid.

Compounds of general formula XXXVI may be prepared by treating an amide or sulphonamide derivative represented by general formula XXVI, wherein X is as defined in general formula I, with a suitable halogenating agent, for example a compound of general formula XVII wherein Hal is fluoride, chloride, bromide or iodide in the presence of a suitable radical initiator (e.g. 2,2'-azobis(2-methylpropionitrile)) in a suitable solvent (e.g. benzene or carbon tetrachloride).

Compounds of general formula XXVI may be prepared by treating p-toluenecarbonyl chloride or p-toluenesulphonyl chloride with N,O-dimethylhydroxylamine in the presence of a suitable base (e.g. triethylamine).

Compounds of general formula XXXVII may be prepared by treating a nitro derivative represented by general formula XXXIV with a compound of general formula XXXVIII

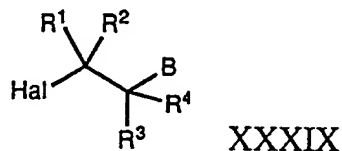


wherein X is as defined in general formula I.

Amino compounds of general formula XXXVIII can be prepared by treatment of a compound of general formula XXXVI with hexamethylenetetramine followed by treatment with ethanolic hydrochloric acid or by sequential treatment of a compound of general formula XXXVI with sodium azide followed by

triphenylphosphine in wet tetrahydrofuran or by hydrogenation over a suitable catalyst.

Compounds of general formula V may be prepared by treating a halo derivative represented by general formula XXXIX



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and B are as defined in general formula I, with a suitable metal (e.g. lithium or magnesium) or with an alkyl lithium. Compounds of general formula XXXIX are available in the art or may be prepared by methods known to those skilled in the art.

The appropriate solvents employed in the above reactions are solvents wherein the reactants are soluble but do not react with the reactants. The preferred solvents vary from reaction to reaction and are readily ascertained by one of ordinary skill in the art.

Compounds of general formulae II, III, and IV are valuable intermediates in the preparation of compounds of general formula I, as are other novel compounds specifically or generically disclosed herein. According to a third aspect of the invention, there is therefore provided a compound of general formula II. According to a fourth aspect of the invention, there is provided a compound of general formula III. According to a fifth aspect of the invention, there is provided a compound of general formula IV.

This invention also relates to a method of treatment for patients (or animals including mammalian animals raised in the dairy, meat, or fur trades or as pets) suffering from disorders or diseases which can be attributed to PAF as previously described, and more specifically, a method of treatment involving the administration of PAF antagonists of general formula I as the active ingredient. In addition to the treatment of warm blooded animals such as mice, rats, horses, cattle, pigs, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

According to a sixth aspect of the invention there is provided a compound of

general formula I for use in human or veterinary medicine particularly in the management of diseases mediated by PAF; compounds of general formula I can be used among other things to reduce inflammation and pain, to correct respiratory, cardiovascular, and intravascular alterations or disorders, and to regulate the activation or coagulation of platelets, to correct hypotension during shock, the pathogenesis of immune complex deposition and smooth muscle contractions.

According to an seventh aspect of the invention there is provided the use of a compound of general formula I in the preparation of an agent for the treatment or prophylaxis of PAF-mediated diseases, and/or the treatment of inflammatory disorders; such as rheumatoid arthritis, osteoarthritis and eye inflammation, cardiovascular disorder, thrombocytopenia, asthma, endotoxin shock, adult respiratory distress syndrome, glomerulonephritis, immune regulation, gastric ulceration, transplant rejection, psoriasis, allergic dermatitis, urticaria, multiple sclerosis, cerebral, myocardial and renal ischemia and any other condition in which PAF is implicated.

Compounds of general formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

According to an eighth aspect of the invention there is provided a pharmaceutical or veterinary formulation comprising a compound of general formula I and a pharmaceutically and/or veterinarily acceptable carrier. One or more compounds of general formula I may be present in association with one or more non-toxic pharmaceutically and/or veterinarily acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients.

The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method

known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose

any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical application to the skin compounds of general formula I may be made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia.

For topical applications to the eye, compounds of general formula I may be made up into a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives, for instance buffers, preservatives including bactericidal and fungicidal agents, such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorohexidine, and thickening agents such as hypromellose may also be included.

Compounds of general formula I may be administered parenterally in a sterile medium. The drug depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

Compounds of general formula I may be used for the treatment of the respiratory tract by nasal or buccal administration of, for example, aerosols or sprays which can disperse the pharmacological active ingredient in the form of a powder or in the form of drops of a solution or suspension. Pharmaceutical compositions with powder-dispersing properties usually contain, in addition to the active ingredient, a liquid propellant with a boiling point below room temperature and, if desired, adjuncts, such as liquid or solid non-ionic or anionic surfactants and/or diluents. Pharmaceutical compositions in which the pharmacological active ingredient is in solution contain, in addition to this, a suitable propellant, and furthermore, if necessary, an additional solvent and/or a stabiliser. Instead of the propellant,

compressed air can also be used, it being possible for this to be produced as required by means of a suitable compression and expansion device.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 1.0 mg to about 3.5 g per patient per day). The dosage employed for the topical administration will, of course, depend on the size of the area being treated. For the eyes each dose will be typically in the range from 10 to 100 mg of the drug.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

It is found that the compounds of general formula I exhibit *in vitro* antagonistic activities with respect to PAF. Compounds of general formula I inhibit PAF-induced functions in both the cellular and tissue levels by changing the PAF binding to its specific receptor site. The ability of compounds of general formula I to inhibit the binding of PAF to its specific receptor binding site on human platelet plasma membranes is measured according to Example 16.

The following examples illustrate the invention, but are not intended to limit the scope in any way.

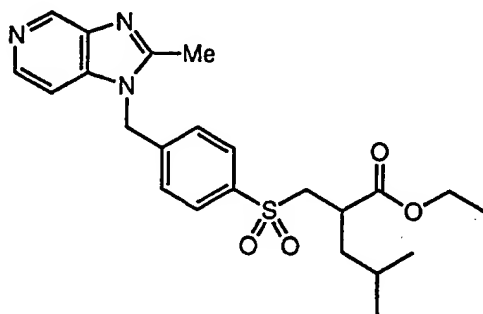
The following abbreviations are used in the Examples:-

DCM - Dichloromethane  
 DMF - Dimethylformamide  
 NBS - N-Bromosuccinimide  
 THF - Tetrahydrofuran

Column chromatography was performed with "flash" grade silica gel. Unless otherwise stated anhydrous magnesium sulphate or anhydrous sodium sulphate was used for drying organic solutions. Unless otherwise stated  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AC-250 spectrometer at 250 MHz and 62.9 MHz respectively using  $\text{CDCl}_3$  as a solvent and internal reference and are reported as  $\delta$  ppm from TMS.

### Example 1

Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate



(a) t-Butyl 2-(4-methylphenylsulphonyl)ethanoate

n-Butyllithium (1.6 M in hexane; 34.8 ml, 55.6 mmol) was added to a stirred solution of methyl 4-methylphenylsulphone (8.7 g, 50.5 mmol) in dry THF (250 ml) at  $-78^\circ\text{C}$ . The reaction mixture turned a yellow colour and after stirring for 0.5 h at  $-78^\circ\text{C}$  a solution of di-t-butyl dicarbonate (5.5 g, 25.3 mmol) in dry THF (15 ml) was added. The mixture was stirred at  $-78^\circ\text{C}$  for 1 h, allowed to warm to room temperature and stirred for 3 h. Ethyl acetate and aqueous ammonium chloride were added. The organic layer was separated, dried, filtered and evaporated. Chromatography (20-60% ethyl acetate in hexane) gave t-butyl 2-(4-methylphenylsulphonyl)ethanoate (6.17 g, 90%) as a colourless oil.

$\delta_{\text{H}}$  (400 MHz) 7.82 (2H, d), 7.36 (2H, d), 4.00 (2H, s), 2.45 (3H, s), 1.39 (9H, s).

## (b) t-Butyl 2-(4-methylphenylsulphonyl)-3-(t-butoxycarbonyl)-5-methylhexanoate

Potassium t-butoxide (3.11 g, 27.4 mmol) was added to a stirred solution of t-butyl 2-(4-methylphenylsulphonyl)ethanoate (6.17 g, 22.8 mmol) in dry DMF (100 ml). The mixture was stirred at room temperature for 10 min and t-butyl 2-bromo-4-methylpentanoic acid (6.88 g, 27.4 mmol) added. The mixture was stirred at room temperature for 48 h and ethyl acetate and aqueous ammonium chloride added. The organic layer was separated, washed with water, dried, filtered and evaporated. Chromatography (0-20% ethyl acetate in hexane) gave t-butyl 2-(4-methylphenylsulphonyl)-3-(t-butoxycarbonyl)-5-methylhexanoate (7.3 g, 72%) as a colourless oil.

$\delta_H$  (400 MHz) 7.78 (2H, dd), 7.33 (2H, d), 4.24 (0.5H, d), 4.11 (0.5H, m), 3.14 (0.5H, m), 2.97 (0.5H, m), 2.45 (3H, s), 1.98-1.22 (21H, m), 0.98-0.82 (6H, m).

## (c) 2-(4-Methylphenylsulphonyl)-3-(hydroxycarbonyl)-5-methylhexanoic acid

Trifluoroacetic acid (31.2 ml, 406 mmol) was added dropwise to a stirred solution of t-butyl 2-(4-methylphenylsulphonyl)-3-(t-butoxycarbonyl)-5-methylhexanoate (7.3 g, 16.5 mmol) in DCM (18 ml). The mixture was stirred at room temperature for 3 h, and DCM and brine were added. The organic layer was separated, dried, filtered and evaporated to give 2-(4-methylphenylsulphonyl)-3-(hydroxycarbonyl)-5-methylhexanoic acid (4.27 g, 78%) as a pale brown oil.

$\delta_H$  (400 MHz) 7.78 (2H, dd), 7.37 (2H, d), 4.56 (0.6H, d), 4.30 (0.4H, m), 3.39-3.15 (1H, m), 2.46 (3H, s), 1.90-1.55 (3H, m), 1.00-0.87 (6H, m).

## (d) 3-(4-Methylphenylsulphonyl)-2-(2-methylpropyl)propanoic acid

A mixture of 2-(4-methylphenylsulphonyl)-3-(hydroxycarbonyl)-5-methylhexanoic acid (4.27 g, 13.0 mmol) and sodium hydrogen carbonate (10.92 g, 130 mmol) in DMF (20 ml) was heated at 100°C for 10 h. The mixture was allowed to stand at room temperature for 8 h and ethyl acetate and 2N hydrochloric acid added. The organic layer was separated, washed with water, dried, filtered and concentrated. Chromatography (1% methanol in DCM) gave 3-(4-methylphenylsulphonyl)-2-(2-methylpropyl)propanoic acid (1.24 g, 34%) as a colourless oil.

$\delta_{\text{H}}$  (400 MHz) 8.01 (1H, s), 7.80 (2H, dd), 7.35 (2H, d), 3.82 (1H, dd), 3.07 (1H, dd), 2.99-2.90 (1H, m), 2.44 (3H, s), 1.67-1.53 (2H, m), 1.43-1.34 (1H, m), 0.89 (3H, d), 0.82 (3H, d).

(e) Ethyl 3-(4-methylphenylsulphonyl)-2-(2-methylpropyl)propanoate

A solution of 3-(4-methylphenylsulphonyl)-2-(2-methylpropyl)propanoic acid (1.2 g, 4.48 mmol), p-toluene sulphonic acid (4 mg) in ethanol (3.5 ml) and toluene (20 ml) was heated at reflux overnight in a Dean-Stark apparatus. The reaction was cooled and ethyl acetate and brine added. The organic layer was separated, dried and evaporated. Chromatography (10-20% ethyl acetate in hexane followed by 5% methanol in DCM) gave ethyl 3-(4-methylphenylsulphonyl)-2-(2-methylpropyl)propanoate (415 mg, 30%) as a colourless oil.

$\delta_{\text{H}}$  7.80 (2H, dd), 7.36 (2H, d), 4.00-3.97 (2H, m), 3.64 (1H, dd), 3.06 (1H, dd), 3.00-2.89 (1H, m), 2.46 (3H, s), 1.65-1.45 (2H, m), 1.44-1.30 (1H, m), 1.24 (3H, t), 0.92 (3H, d), 0.86 (3H, d).

(f) Ethyl 3-(4-bromomethylphenylsulphonyl)-2-(2-methylpropyl)propanoate

To a solution of ethyl 3-(4-methylphenylsulphonyl)-2-(2-methylpropyl)propanoate (415 mg, 1.32 mmol) in carbon tetrachloride (20 ml) and NBS (238 mg, 1.32 mmol) heated at reflux was added 2,2'-azobis(isobutyronitrile) (10 mg). The mixture was heated at reflux overnight and allowed to cool to room temperature. DCM and water were added and the organic layer separated, dried, filtered and evaporated. Chromatography (10% ethyl acetate in hexane) gave ethyl 3-(4-bromomethylphenylsulphonyl)-2-(2-methylpropyl)propanoate (209 mg, 53%) as an amorphous solid.

$\delta_{\text{H}}$  7.80 (2H, dd), 7.40 (2H, d), 4.52 (2H, s), 4.08-3.97 (2H, m), 3.70 (1H, dd), 3.08 (1H, dd), 3.03-2.90 (1H, m), 1.65-1.30 (3H, m), 1.26 (3H, t), 0.95 (3H, d), 0.87 (3H, d).

(g) Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate

Sodium hydride (60% dispersion in oil) (20 mg, 0.51 mmol) was added to a stirred solution of 2-methylimidazo[4,5-c]pyridine (64 mg, 0.48 mmol) in a

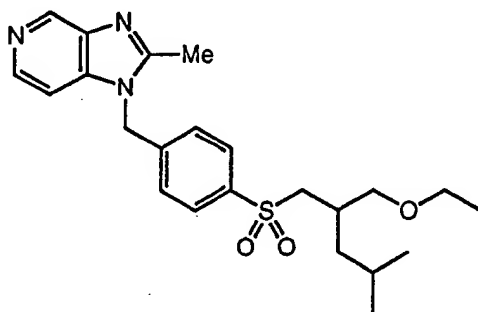
mixture of dry THF (10 ml) and dry DMF (10 ml) under argon at room temperature. After 1 h a solution of ethyl 3-(4-bromomethylphenylsulphonyl)-2-(2-methylpropyl)propanoate (186 mg, 0.48 mmol) in dry THF (2 ml) was added. The mixture was stirred for 8 h and the solvent was removed under reduced pressure, saturated ammonium chloride was added and the product was extracted with ethyl acetate. The combined organic layers were washed with water, dried, filtered and the solvent was removed. Chromatography (8% methanol in DCM) gave three regioisomers, ethyl 3-(4-(3H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate which elutes first, ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate which elutes second and ethyl 3-(4-(5H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate which elutes last. The desired regioisomer, ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate (7 mg, 3%), was obtained as a colourless oil.

$\delta_H$  9.03 (1H, s), 8.37 (1H, d), 7.78 (2H, dd), 7.35-7.11 (3H, m), 5.39 (2H, s), 4.05-3.95 (2H, m), 3.65 (1H, dd), 3.05 (1H, dd), 3.00-2.88 (1H, m), 1.70-1.30 (3H, m), 1.20 (3H, t), 0.97 (3H, d), 0.90 (3H, d).

Although not claimed in this patent application the other two regioisomers are antagonists of platelet activating factor.

### Example 2

1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)propane



(a) N,O-Dimethyl-N-4-methylphenylsulphonyl hydroxylamine

To a solution of triethylamine (26.6 ml, 0.192 mol) in dry THF (200 ml) is added powdered N,O-dimethylhydroxylamine hydrochloride (9.36 g, 0.096 mol) in one portion. The mixture is stirred at room temperature for 0.5 h and powdered 4-methylphenylsulphonyl chloride (18.3 g, 0.096 mol) is added in one portion. The mixture is stirred overnight at room temperature. Saturated ammonium chloride (100 ml) is added and the mixture is extracted with ethyl acetate (3 x 100 ml), the organics are dried, filtered and evaporated. The resulting oil is chromatographed (ethyl acetate in hexane) to give N,O-dimethyl-N-4-methylphenylsulphonyl hydroxylamine the structure of which is confirmed by  $^1\text{H}$  n.m.r. spectroscopy.

(b) 1-Ethoxy-2-(2-methylpropyl)-3-(4-methylphenylsulphonyl)propane

A solution of N,O-dimethyl-N-4-methylphenylsulphonyl hydroxylamine (17.2 g, 0.08 mol) in dry THF (50 ml) is added dropwise to a stirred solution of 1-lithio-2-(2-methylpropyl)-3-ethoxypropane (prepared from lithium (0.70 g, 0.1 mol) and 1-bromo-2-(2-methylpropyl)-3-ethoxypropane (22.2 g, 0.1 mol) with sonication) in dry THF (150 ml) at  $0^\circ\text{C}$  under argon. The mixture is allowed to slowly warm up to room temperature and is stirred overnight. Saturated ammonium chloride (100 ml) is added and the product is extracted with ethyl acetate (3 x 100 ml). The combined organic layers are washed with water (2 x 100 ml), are dried, filtered and the solvent is removed. Chromatography (ethyl acetate in hexane) gives 1-ethoxy-2-(2-methylpropyl)-3-(4-methylphenylsulphonyl)propane the structure of which is confirmed by  $^1\text{H}$  n.m.r. spectroscopy.

(c) 1-Ethoxy-2-(2-methylpropyl)-3-(4-bromomethylphenylsulphonyl)propane

To a solution of 1-ethoxy-2-(2-methylpropyl)-3-(4-methylphenylsulphonyl)propane (14.9 g, 0.05 mol) in benzene (50 ml) and NBS (8.9 g, 0.05 mol) heated at reflux is added 2,2'-azobis(2-methylpropionitrile) (50 mg). The mixture is heated at reflux for 12 h and is allowed to cool to room temperature. The white precipitate of succinimide that forms is separated and discarded. The filtrate is taken up in DCM (100 ml) and is washed with water (3 x 50 ml) followed by brine (50 ml) and is dried. Filtration, concentration and subsequent chromatography (ethyl acetate in hexane) gives 1-ethoxy-2-(2-methylpropyl)-3-(4-bromomethylphenylsulphonyl)propane the structure of which is confirmed by

<sup>1</sup>H n.m.r. spectroscopy.

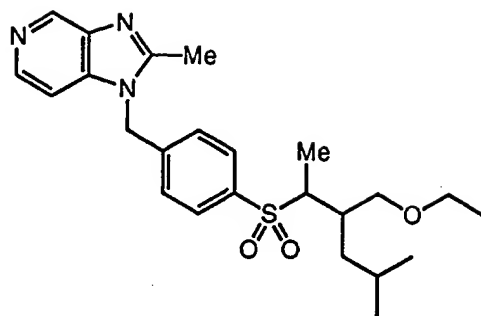
(d) 1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)propane

Sodium hydride (60% dispersion in oil) (204 mg, 5.1 mmol) is added to a stirred solution of 2-methylimidazo[4,5-c]pyridine (640 mg, 4.8 mmol) in a mixture of dry THF (40 ml) and dry DMF (10 ml) under argon at room temperature. After 1 h a solution of 1-ethoxy-2-(2-methylpropyl)-3-(4-bromomethyl-phenylsulphonyl)propane (1.80 g, 4.8 mmol) in dry THF (15 ml) is added. The mixture is stirred for 8 h and the solvent is removed under reduced pressure, saturated ammonium chloride (60 ml) is added and the product is extracted with ethyl acetate (3 x 60 ml). The combined organic layers are washed with water (2 x 50 ml), dried, filtered and the solvent is removed. Chromatography (8% methanol in DCM) gives three regioisomers, 1-ethoxy-2-(2-methylpropyl)-3-(4-(3H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)propane which elutes first, 1-ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)propane which elutes second and 1-ethoxy-2-(2-methylpropyl)-3-(4-(5H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)propane which elutes last. The structure of the desired regioisomer 1-ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)propane is confirmed by <sup>1</sup>H n.m.r. spectroscopy. Although not claimed in this patent application the other two regioisomers 1-ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)propane and 1-ethoxy-2-(2-methylpropyl)-3-(4-(5H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)propane are antagonists of platelet activating factor.

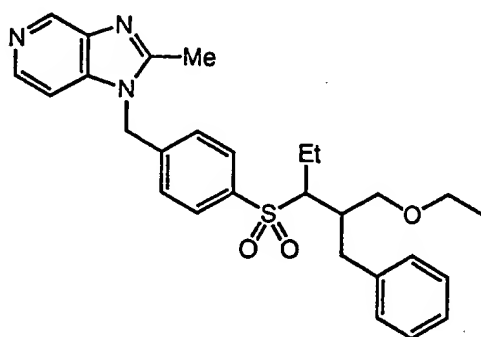
### Examples 3-15

The compounds of Examples 3 to 15 are prepared by procedures analogous to the methods of Example 1 and/or Example 2 employing the appropriate starting materials. The structure of each compound is confirmed by <sup>1</sup>H n.m.r. spectroscopy.

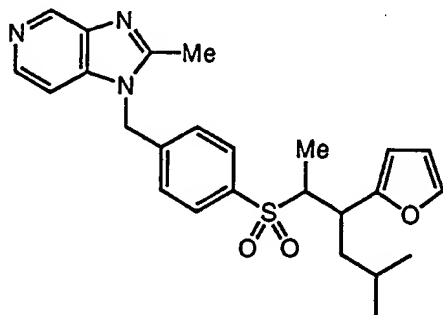
3. 1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)butane



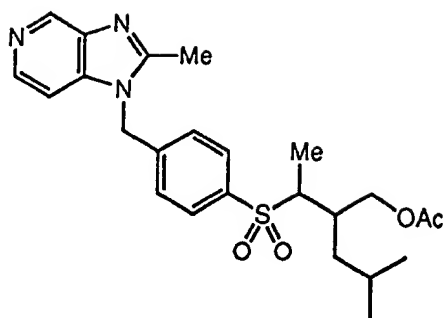
4. 1-Ethoxy-2-benzyl-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)pentane



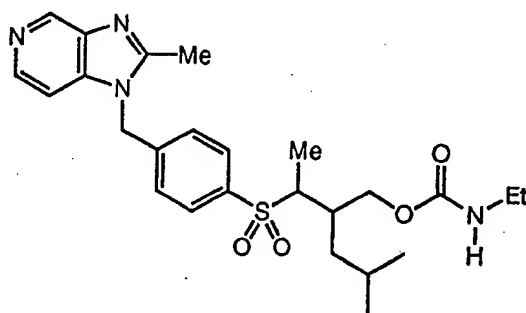
5. 1-Methyl-1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)-2-(furan-2-yl)-4-methylpentane



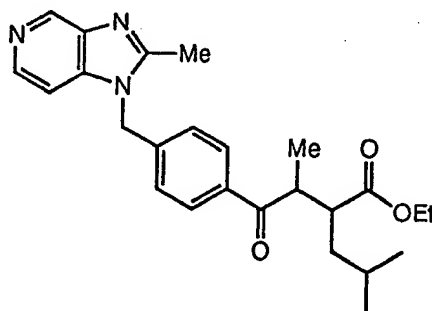
6. 3-Acetoxy-5-methyl-2-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)hexane



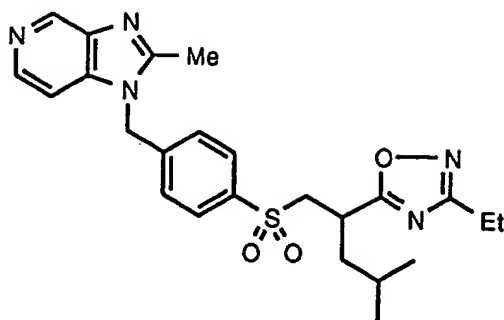
7. 3-Ethylcarbamoyl-5-methyl-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)hexane



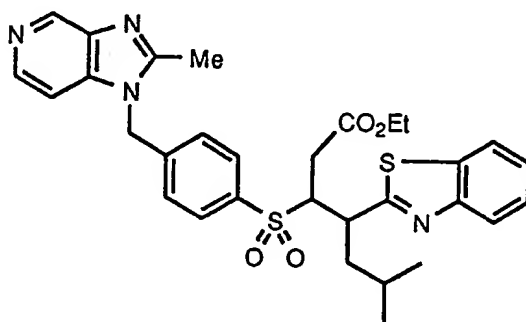
8. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylcarbonyl)-2-(2-methylpropyl)butanoate



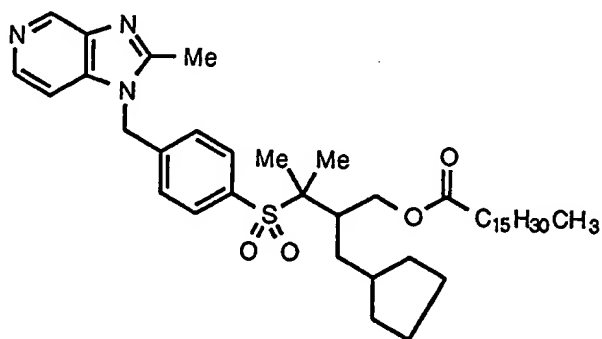
9. 1-(4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)-2-(3-ethyl-1,2,4-oxadiazol-5-yl)-4-methylpentane



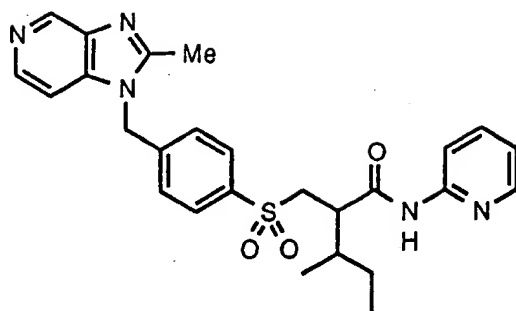
10. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-4-benzthiazol-2-yl-5-methylhexanoate



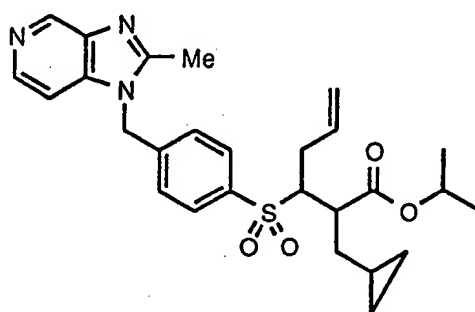
11. 1-Heptadecanoyl-2-(2-cyclopentylmethyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-3-methylbutane



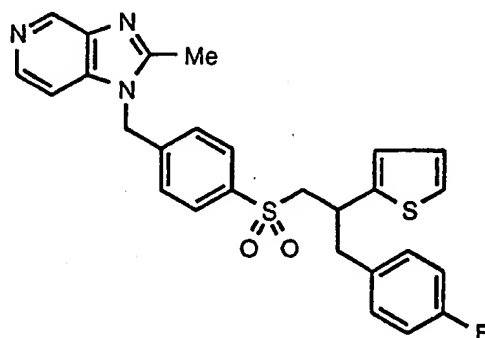
12. N-2-Pyridinyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(1-methylpropyl)propionamide



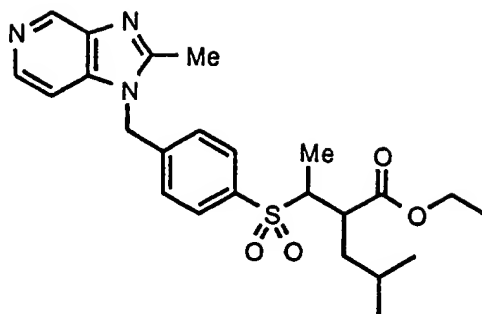
13. i-Propyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(cyclopropylmethyl)hex-5-enoate



14. 1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-thienyl)-3-(4-fluorophenyl)ethane



15. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)butanoate



### Example 16

#### Inhibition of [ $^3\text{H}$ ]-PAF Receptor Binding

The inhibition of [ $^3\text{H}$ ]-PAF binding to human platelet plasma membrane by compounds of general formula I is determined by isotopic labelling and filtration techniques. Platelet concentrates are obtained from a hospital blood bank. These platelet concentrates (500-2500 ml.) are centrifuged at 800 rpm for 10 minutes in a SORVALL RC3B centrifuge to remove the red blood cells present. (The word SORVALL is a trade mark.) The supernatant is subsequently centrifuged at 3,000 rpm in a SORVALL RC3B centrifuge to pellet the platelets present. The platelet rich pellets are resuspended in a minimum volume of buffer (150 mM NaCl, 10 mM Tris, 2 mM EDTA, pH 7.5) and layered onto Ficoll-Paque gradients, 9 ml platelet concentrate to 2 ml Ficoll, and centrifuged at 1,900 rpm for 15 minutes in a SORVALL RT6000 centrifuge. This step removes the residual red blood cells and other nonspecific material such as lymphocytes from the preparation. The platelets which form a band between the plasma and the Ficoll are removed, resuspended in the above buffer and centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge. The pelleted platelets are resuspended in buffer (10 mM Tris, 5 mM  $\text{MgCl}_2$ , 2 mM EDTA, pH 7.0), snap frozen in liquid  $\text{N}_2$  and allowed to thaw slowly at room temperature in order to lyse the platelets. The latter step is repeated at least 3 times to ensure proper lysis. The lysed platelets are centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge and resuspended in buffer. The latter step is repeated twice in order to remove any cytoplasmic proteins which may hydrolyse the platelet activating factor (PAF) receptor. The prepared platelet membranes may be stored at  $-70^\circ\text{C}$ . After thawing the prepared membranes are centrifuged in a SORVALL RT6000 at 3,000 rpm for 10 minutes and resuspended in assay buffer.

The assay is conducted by preparing a series of Tris-buffered solutions of the

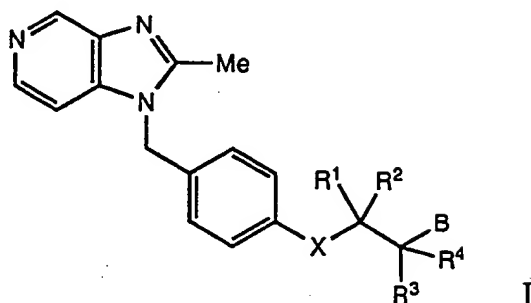
selected antagonist of predetermined concentrations. Each of these solutions contained [ $^3\text{H}$ ]-PAF (0.5 nM; 1-*O*-[ $^3\text{H}$ ]octadecyl-2-acetyl-*sn*-glycero-3-phosphoryl choline with a specific activity of 132 Ci/mmol), unlabelled PAF (1000 nM), a known amount of the test antagonist, and a sufficient amount of Tris-buffer solution (10 mM Tris, 5 mM  $\text{MgCl}_2$ , pH 7.0, 0.25% BSA) to make the final volume 1 ml. Incubation is initiated by the addition of 100  $\mu\text{g}$  of the isolated membrane fraction to each of the above solutions at  $0^\circ\text{C}$ . Two control samples, one (C1) which contained all the ingredients described above except the antagonist and the other (C2) contains C1 plus a 1000-fold excess of unlabelled PAF, are also prepared and incubated simultaneously with the test samples. After 1 hour incubation, each solution is filtered rapidly under vacuo through a WHATMAN GF/C glass fibre filter in order to separate unbound PAF from bound PAF. (The word WHATMAN is a trade mark.) The residue in each case is rapidly washed 4 times with 5 ml cold ( $4^\circ\text{C}$ ) Tris-buffer solution. Each washed residue is dried under vacuum on a sampling manifold and placed into vials containing 20 ml of OPTIPHASE MP scintillation fluid and the radioactivity counted in a liquid scintillation counter. (The word OPTIPHASE is a trade mark.) Defining the counts for total binding with antagonist from a test sample as "TBA"; the counts for total binding from the control sample C1 as "TB"; and the counts for nonspecific binding from the control sample C2 as "NSB", the percent inhibition of each test antagonist can be determined by the following equation:

$$\% \text{Inhibition} = [(TB - TBA) / SB] \times 100$$

where the specific binding  $SB = TB - \text{NSB}$

CLAIMS

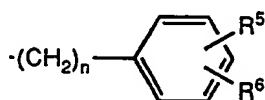
1. A compound of general formula I;



wherein:

X represents a  $-C(=O)-$ ,  $-C(=S)-$ ,  $-S(\rightarrow O)-$  or  $-S(=O)_2-$  group;

$R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  each independently represents hydrogen,  $-C_1-C_6$  alkyl optionally substituted by one or more halogen atoms,  $-C_2-C_6$  alkenyl,  $-C_2-C_6$  alkynyl,  $-(C_1-C_6 \text{ alkyl})CO_2C_1-C_6 \text{ alkyl}$ ,  $-(C_1-C_6 \text{ alkyl})SC_1-C_6 \text{ alkyl}$ ,  $-(C_1-C_6 \text{ alkyl})OC_1-C_6 \text{ alkyl}$ ,  $-(C_1-C_6 \text{ alkyl})N(C_1-C_6 \text{ alkyl})_2$ ,  $-C_3-C_8$  cycloalkyl,  $-C_4-C_8$  cycloalkenyl,  $-(C_1-C_6 \text{ alkyl})C_3-C_8$  cycloalkyl,  $-(C_1-C_6 \text{ alkyl})C_4-C_8$  cycloalkenyl,  $-(C_1-C_6 \text{ alkyl})OC_3-C_8$  cycloalkyl,  $-(C_1-C_6 \text{ alkyl})OC_4-C_8$  cycloalkenyl,  $-(C_1-C_6 \text{ alkyl})SC_3-C_8$  cycloalkyl,  $-(C_1-C_6 \text{ alkyl})SC_4-C_8$  cycloalkenyl, a side chain of a naturally occurring amino acid or a group D wherein D represents a group:



wherein  $n$  is an integer from 0 to 3, and each of  $R^5$  and  $R^6$  is independently hydrogen,  $-C_1-C_6$  alkyl,  $-C_2-C_6$  alkenyl,  $-C_2-C_6$  alkynyl, halogen,  $-CN$ ,  $-CO_2H$ ,  $-CO_2C_1-C_6 \text{ alkyl}$ ,  $-CONH_2$ ,  $-CONHC_1-C_6 \text{ alkyl}$ ,  $-CONH(C_1-C_6 \text{ alkyl})_2$ ,  $-CHO$ ,  $-CH_2OH$ ,  $-CF_3$ ,  $-OC_1-C_6 \text{ alkyl}$ ,  $-SC_1-C_6 \text{ alkyl}$ ,  $-SOC_1-C_6 \text{ alkyl}$ ,  $-SO_2C_1-C_6 \text{ alkyl}$ ,  $-NH_2$  or  $-NHCOMe$ ;

or any combination of  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  together with the atoms to which they are attached form a 5 to 8 membered heterocyclic ring;

or any combination of  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  together with the carbon atom to which they are attached form a  $C_3-C_8$  cycloalkyl ring;

B represents a) a  $-(CH_2)_m A$  group wherein m is an integer from 0 to 1 and the group A represents a 5- or 6-membered heterocyclic ring, which heterocyclic ring may be optionally fused to a benzene ring or to a further 5-, 6- or 7-membered heterocyclic ring containing one or more nitrogen atoms, wherein at least one of the said heterocyclic rings may also contain an oxygen or sulphur atom, and wherein any of the rings may be optionally substituted with one or more substituents selected from hydrogen, halogen,  $-C_1-C_4$  perfluoroalkyl, hydroxyl, carbonyl, thiocarbonyl, carboxyl,  $-CONH_2$ , a group -D wherein D is as defined above,  $-R^7$ ,  $-OR^7$ ,  $-SR^7$ ,  $-SOR^7$ ,  $-SO_2R^7$ ,  $-NHR^7$ ,  $-NR^7R^7$ ,  $-CO_2R^7$  or  $-CONHR^7$  wherein  $R^7$  is  $-C_1-C_6$  alkyl,  $-C_2-C_6$  alkenyl,  $-C_2-C_6$  alkynyl,  $-C_3-C_8$  cycloalkyl or  $-C_4-C_8$  cycloalkenyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxyl, amino, carboxyl,  $-C_1-C_4$  perfluoroalkyl,  $-C_1-C_6$  alkyl,  $-C_2-C_6$  alkenyl,  $-C_2-C_6$  alkynyl,  $-C_3-C_8$  cycloalkyl,  $-C_4-C_8$  cycloalkenyl,  $-OC_1-C_6$  alkyl,  $-SC_1-C_6$  alkyl, tetrazol-5-yl, a group -D wherein D is as defined above or a heteroaryl or heteroarylmethyl group;

b) a  $ZR^8$  group wherein Z is  $-C(=O)-$ ,  $-C(=O)O-$ ,  $-C(=O)S-$ ,  $-CH_2O-$ ,  $-CH_2OC(=O)-$ ,  $-C(=S)-$ ,  $-C(=S)O-$ ,  $-CH_2S-$ ,  $-CH_2OC(=O)C(=O)O-$ ,  $-CH_2OSO_2-$ ,  $-NHC(=O)O-$ ,  $-CH_2OC(=O)NH-$  or  $-CH_2C(=O)O-$  group and  $R^8$  is hydrogen,  $-C_1-C_{18}$  alkyl,  $-C_2-C_{18}$  alkenyl,  $-C_2-C_{18}$  alkynyl,  $-(C_1-C_6 \text{ alkyl})OC_1-C_6 \text{ alkyl}$ ,  $-(C_1-C_6 \text{ alkyl})SC_1-C_6 \text{ alkyl}$ ,  $-(C_1-C_6 \text{ alkyl})O(C_1-C_6 \text{ alkyl})OC_1-C_6 \text{ alkyl}$ ,  $-C_3-C_8$  cycloalkyl,  $-C_4-C_8$  cycloalkenyl, a group D as defined above or a group A as defined above;

c) a  $-CH_2NR^9R^{10}$  group or a  $-CONR^9R^{10}$  group wherein each of  $R^9$  and  $R^{10}$  is independently hydrogen,  $-C_1-C_6$  alkyl,  $-C_3-C_8$  cycloalkyl, pyridinyl, a group D as defined above or  $R^9$  and  $R^{10}$  together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

2. A compound as claimed in Claim 1, in which X represents a  $-C(=O)-$  group or a  $-S(=O)_2-$  group.

3. A compound as claimed in Claims 1 and 2, wherein  $R^1$  represents a hydrogen atom, a  $-C_1-C_6$  alkyl (for example methyl or ethyl) group, a  $-C_2-C_6$  alkenyl (for

example allyl) group or a  $-(C_1-C_6 \text{ alkyl})CO_2C_1-C_6 \text{ alkyl}$  (for example ethoxycarbonylmethyl) group.

4. A compound as claimed in any one of Claim 1 to 3, wherein  $R^2$  represents a hydrogen atom or a  $-C_1-C_6 \text{ alkyl}$  group.

5. A compound as claimed in 1 to 4, wherein  $R^3$  represents a side chain of a naturally occurring amino acid, a  $-(C_1-C_6 \text{ alkyl})C_3-C_8 \text{ cycloalkyl}$  group or a group D.

6. A compound as claimed in any one of Claims 1 to 5, wherein  $R^4$  represents a hydrogen atom.

7. A compound as claimed in any one of Claims 1 to 6, wherein, in the group D, n represents an integer of 1,  $R^5$  represents a hydrogen atom or a halogen atom and  $R^6$  represents a hydrogen atom.

8. A compound as claimed in any one of Claims 1 to 7, wherein B represents a  $-(CH_2)_m A$  group, a  $ZR^8$  or a  $-CONR^9R^{10}$  group.

9. A compound as claimed in Claim 8, wherein m represents an integer of 0.

10. A compound as claimed in Claim 8, wherein A represents a furanyl group, an oxadiazolyl group, a benzthiazolyl group or a thienyl group.

11. A compound as claimed in Claim 10, wherein  $R^7$  represents a  $-C_1-C_6 \text{ alkyl}$  group.

12. A compound as claimed in Claim 8, wherein Z represents a  $-C(=O)O-$  group, a  $-CH_2O-$  group, a  $-CH_2OC(=O)-$  group or a  $-CH_2OC(=O)NH-$  group.

13. A compound as claimed in Claim 8 or Claim 12, wherein  $R^8$  represents a  $-C_1-C_{18} \text{ alkyl}$  group.

14. A compound as claimed in Claim 8, wherein  $R^9$  represents a pyridinyl group and  $R^{10}$  represents a hydrogen atom.

15. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-

(2-methylpropyl)propanoate,  
 1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl)propane,  
 1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)butane,  
 1-Ethoxy-2-benzyl-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)pentane,  
 1-Methyl-1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)-2-(furan-2-yl)-4-methylpentane,  
 3-Acetoxy-5-methyl-2-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)hexane,  
 3-Ethylcarbamoyl-5-methyl-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)hexane,  
 Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylcarbonyl)-2-(2-methylpropyl)butanoate,  
 1-(4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)-2-(3-ethyl-1,2,4-oxadiazol-5-yl)-4-methylpentane,  
 Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-4-benzthiazol-2-yl-5-methylhexanoate,  
 1-Heptadecanoyl-2-(2-cyclopentylmethyl)-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)-3-methylbutane,  
 N-2-Pyridinyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(1-methylpropyl)propionamide,  
 i-Propyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(cyclopropylmethyl)hex-5-enoate,  
 1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-thienyl)-3-(4-fluorophenyl)ethane,  
 Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)butanoate,

or a salt of such a compound.

16. A compound as claimed in any one of Claims 1 to 15 for use in human or veterinary medicine, particularly in the management of diseases or conditions mediated by platelet activating factor.

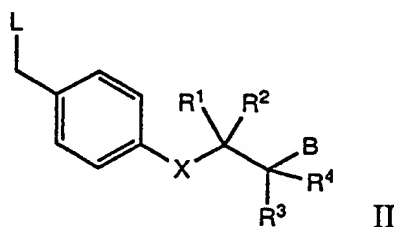
17. The use of a compound as claimed in any one of Claims 1 to 15 in the preparation of an agent for the treatment or prophylaxis of diseases or conditions

mediated by platelet activating factor.

18. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of Claims 1 to 15 and a pharmaceutically and/or veterinarily acceptable carrier.

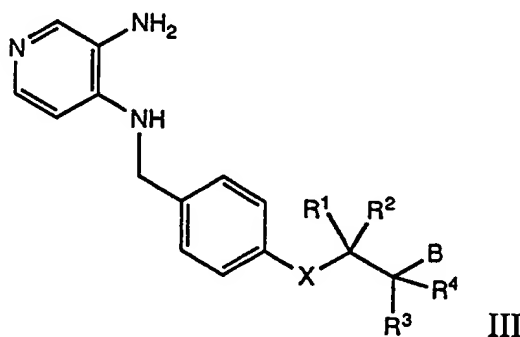
19. A process for preparing a compound of general formula I as defined in Claim 1, the process comprising:

(a) treating 2-methylimidazo[4,5-c]pyridine with a base followed by a benzyl derivative of general formula II



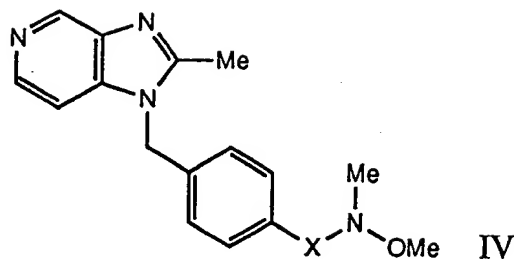
wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and B are as defined in general formula I, and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy; or

(b) treating a diamino derivative represented by general formula III

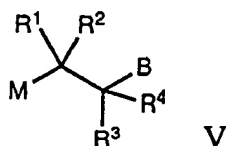


wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , X and B are as defined in general formula I, with acetic acid or a suitable derivative thereof; or

(c) treating an amido or sulphonamido derivative represented by general formula IV



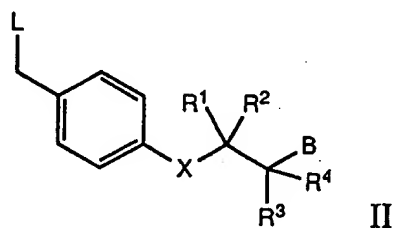
wherein X is as defined in general formula I, with a compound of general formula V



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and B are as defined in general formula I, and M is MgBr or Li; or

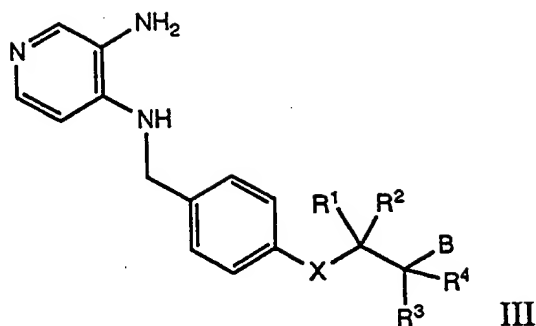
(d) optionally after step (a), step (b) or step (c) converting, in one or a plurality of steps, a compound of general formula I into another compound of general formula I.

20. A benzyl derivative of general formula II



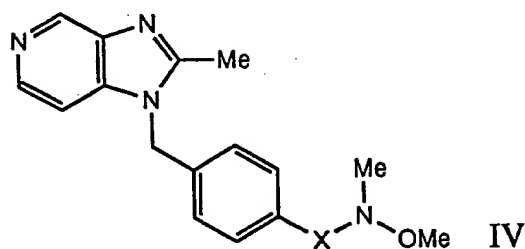
wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and B are as defined in general formula I, and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy.

21. A compound of general formula III



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, X and B are as defined in general formula I.

22. A compound of general formula IV



wherein X is as defined in general formula I.

23. A method for the treatment or prophylaxis of diseases or physiological conditions of humans or mamalian animals mediated by platelet activating factor, comprising administering to the patient an amount of a compound as claimed in any of claims 1 to 15 effective to antagonise the effects of platelet activating factor on target cells responsible for such diseases or physiological conditions.

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**Patents Act 1977**  
**Examiner's report to the Comptroller and**  
**Section 17 (The Search Report)**

Application number

GB 9302730.8

**Relevant Technical fields**

(i) UK Cl (Edition L ) C2C CQN CQT CRA CRG CUL

(ii) Int Cl (Edition 5 ) C07D

**Databases (see over)**

(i) UK Patent Office

(ii) ONLINE DATABASE: CAS ONLINE

**Search Examiner**

D S LUCAS

**Date of Search**

Documents considered relevant following a search in respect of claims 1 TO 19 AND 23

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
A	WO 91/17157 A (BRITISH BIO-TECHNOLOGY LTD) - see compounds 30-37 on page 9 and Examples 30-37	1-19 and 23

Category	Identity of document and relevant passages	Relevant to claim(s)

### Categories of documents

**X:** Document indicating lack of novelty or of inventive step.

**Y:** Document indicating lack of inventive step if combined with one or more other documents of the same category.

**A:** Document indicating technological background and/or state of the art.

**P:** Document published on or after the declared priority date but before the filing date of the present application.

**E:** Patent document published on or after, but with priority date earlier than, the filing date of the present application.

**&:** Member of the same patent family, corresponding document.

**Databases:** The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).